

dominant note has been that nothing should be done to harm the interests of the patients. This is a sound basis on which the profession can unite in insisting on obtaining for its junior members proper terms and conditions of service.

## Drugs Against Viruses

At the present time antiviral chemotherapy is one of the most rapidly progressing branches of medical science. Drugs of proved efficacy are available commercially and are being used for the prevention and treatment of virus diseases of man. The viruses which have succumbed to the attack include smallpox (both variola major and alastrim), vaccinia, and herpes simplex, and the outlook is promising in the field of influenza and other virus infections of the respiratory tract.

The pioneer observation of the antiviral activity of benzaldehyde thiosemicarbazone and certain of its derivatives made by D. Hamre, J. Bernstein, and R. Donovick<sup>1</sup> in 1950 led over the course of the years to the development of methisazone (Marboran) and its trial in Madras as a prophylactic agent against smallpox in 1963.<sup>2</sup> The final results of this trial have recently been described by D. J. Bauer.<sup>3</sup>

Methisazone was given to 2,287 persons who had been in intimate contact with patients with smallpox. Among them six persons (0.26%) subsequently developed smallpox, of whom two died. Among a group of 2,665 similarly exposed persons who were not treated, there were 105 cases (3.94%), with 18 deaths. The reduction in the incidence of contact cases associated with methisazone treatment was highly significant. Persons who have been in contact with smallpox should be treated with methisazone in order to obtain immediate protection against the exposure which has already taken place, but they should also be vaccinated to confer protection against further exposure which may take place in the near future. The main side-effect of the drug was vomiting.

A similar protective effect of methisazone was also observed by Ribeiro do Valle and co-workers<sup>4</sup> among persons exposed to alastrim infection in São Paulo, Brazil. Thus, among 384 contacts who received treatment with methisazone, mostly in lower doses than those used in the Madras trials, eight developed alastrim, whereas among 520 contacts who received no treatment there were 42 cases. Most of the contacts were not vaccinated or revaccinated after exposure (347 in the treatment group and 449 in the untreated group), so that methisazone in the absence of vaccination was an effective measure from the public-health point of view for reducing the incidence of contact cases and controlling an outbreak.

A prophylactic effect among persons who have been exposed to smallpox has also been obtained with M. and B. 7714 (3-methyl-4-bromo-5-formylisothiazole thiosemicarbazone).<sup>5</sup> Among 196 contacts treated with the drug there were 40 cases

of smallpox, compared with 60 cases among 201 contacts who were left untreated. The difference was significant at the 5% level. The authors state that M. and B. 7714 is not to be recommended in the prophylaxis of smallpox, and that the slightness of the prophylactic effect compared with that of methisazone cannot be ascribed to poor absorption as a consequence of vomiting. But further trial might be appropriate with smaller and more frequent doses in an attempt to reduce vomiting, for in the face of a life-threatening infection such as smallpox the free use of a drug with relatively unimportant side-effects is justifiable.

The lack of success in antiviral chemotherapy up to recent times can probably be ascribed to the fact that antiviral drugs have always been visualized as therapeutic agents. But the results obtained in India and Brazil show that their main application at present is in prophylaxis. The antiviral thiosemicarbazones can act only against virus which has entered cells and is actively multiplying. They therefore protect a smallpox contact by suppressing an infection which is already under way but which has not yet become clinically manifest. If the contact has escaped smallpox infection, then the drugs will naturally do nothing. Chemoprophylaxis with these antiviral agents is really therefore early treatment, but from the public-health point of view it seems justified to retain the term prophylaxis in this special sense because there is no way of telling which contacts are already in the incubation period except by awaiting events.

Some success has also been achieved in the treatment of other virus diseases. Bauer<sup>6</sup> has reported recovery of patients with vaccinia gangrenosa treated with methisazone. Apparent benefit has also been obtained in the treatment of eczema vaccinatum,<sup>6,7</sup> though the course of this disease is so variable that the effect of treatment is difficult to assess. It would seem desirable to investigate the effect of methisazone in this condition by means of a double-blind trial. In a preliminary communication this week in the *B.M.J.* (page 625) Dr. T. F. Sandeman, of Melbourne, reports that some patients with malignant lymphoma improved when given methisazone. Though it is too early to draw any firm conclusions from these results, they will be noted with interest.

Success in the treatment of virus diseases is not confined to the thiosemicarbazones. Idoxuridine<sup>8</sup> is now the established drug for treating herpetic ulcers of the cornea, and it is also active against vaccinia infection. Other drugs which are in the process of development include amantidine hydrochloride, which has some prophylactic effect against influenza, and statolon, a substance which induces cells to manufacture interferon.

## Inappropriate Secretion of Antidiuretic Hormone

A low concentration of sodium in the serum (hyponatraemia) is found in a variety of conditions. It may be associated with excessive loss of sodium in the urine, as in Addison's disease, when there is also hypotension and contraction of the volume of extracellular fluid. It may also occur in oedematous states, such as congestive cardiac failure and portal cirrhosis, in which urinary excretion of sodium is greatly reduced and there is expansion of the volume of extracellular fluid. In recent years a third type of hyponatraemia has been recognized in which, despite normal adrenal and kidney function,

<sup>1</sup> Hamre, D., Bernstein, J., and Donovick, R., *Proc. Soc. exp. Biol. (N.Y.)*, 1950, **73**, 275.

<sup>2</sup> Bauer, D. J., St. Vincent, L., Kempe, C. H., and Downie, A. W., *Lancet*, 1963, **2**, 494.

<sup>3</sup> —, *IV International Congress of Infectious Diseases*, Munich, 26-30 April 1966.

<sup>4</sup> Ribeiro do Valle, L. A., Raposo de Melo, P., de Salles Gomes, L. F., and Morato Proença, L., *Lancet*, 1965, **2**, 976.

<sup>5</sup> Rao, A. R., McKendrick, G. D. W., Velayudhan, L., and Kamalakshi, K., *ibid.*, 1966, **1**, 1072.

<sup>6</sup> Bauer, D. J., *Ann. N.Y. Acad. Sci.*, 1965, **130**, 110.

<sup>7</sup> Adels, B. R., and Oppé, T. E., *Lancet*, 1966, **1**, 18.

<sup>8</sup> Kaufman, H. E., Martola, E.-L., and Dohliman, C., *Arch. Ophthalm.*, 1962, **68**, 235.